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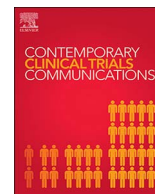
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# Facilitators and barriers to the successful implementation of pediatric antibacterial drug trials: Findings from CTTI's survey of investigators

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## ABSTRACT

An urgent need exists to develop new antibacterial drugs for children. We conducted research with investigators of pediatric antibacterial drug trials to identify facilitators and barriers in the conduct of these trials. Seventy-three investigators completed an online survey assessing the importance of 15 facilitators (grouped in 5 topical categories) and the severity of 36 barriers (grouped in 6 topical categories) to implementing pediatric antibacterial drug trials. Analysis focused on the identification of key factors that facilitate the successful implementation of pediatric antibacterial drug trials and the key barriers to implementation. Almost all investigators identified two factors as very important facilitators: having site personnel for enrollment and having adequate funding. Other top factors were related to staffing. Among the barriers, factors related to parent concerns and consent were prominent, particularly obtaining parental consent when there was disagreement between parents, concerns about the number of blood draws, and concerns about the number of invasive procedures. Having overly narrow eligibility criteria was also identified as a major barrier. The survey findings suggest three areas in which to focus efforts to help facilitate ongoing drug development: (1) improving engagement with parents of children who may be eligible to enroll in a pediatric antibacterial drug trial, (2) broadening inclusion criteria to allow more participants to enroll, and (3) ensuring adequate staffing and establishing sustainable financial strategies, such as funding pediatric trial networks. The pediatric antibacterial drug trials enterprise is likely to benefit from focused efforts by all stakeholders to remove barriers and enhance facilitation.

## 1. Introduction

Before the late 1990s, therapeutic drugs were not regularly evaluated for their safety and efficacy in children, leaving pediatricians to rely largely on data from adult studies, as well as on trial and error, to inform their treatment decisions [1]. In 1997, the U.S. Congress enacted the Food and Drug Administration Modernization Act [2], which encouraged the voluntary conduct of pediatric drug trials and also mandated that pharmaceutical companies conduct pediatric studies in certain situations. In 2002, an amendment called the Best Pharmaceuticals

for Children Act (BPCA) [3,4] provided companies with a financial incentive of market and patent exclusivity if they conduct a pediatric trial at the request of the FDA. In other legislation, the Pediatric Research Equity Act (PREA) of 2003 [3] required that companies developing drugs for adults conduct pediatric trials unless a waiver is obtained.

Since the initiation of BPCA, PREA, and the regulatory requirement to register pediatric drug trials, many such trials have been conducted and drug label updates approved. Between September 27, 2007, and September 10, 2013, 469 pediatric studies were conducted, including

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studies on efficacy and safety, pharmacokinetics and safety, safety exclusively, and studies of other clinical importance to pediatric populations [5]. Additionally, 535 pediatric label changes have been approved as of July 31, 2015 [6]. Yet, an FDA-commissioned review by the National Academy of Medicine (formerly the Institute of Medicine) concluded that challenges remain in the conduct of pediatric drug trials, including the reluctance among parents and physicians to enroll children in trials [7,8].

In the field of antibacterial drug development, the number of new drugs developed has steadily declined over the past several decades [9], and the current pipeline is “alarmingly thin.” [10] There also remains an urgent need for the study of new antibacterial drugs for the pediatric population, especially those that are effective for multidrug-resistant gram negative infections [11]. Conducting antibacterial drug trials with children is more challenging than with adults, making it difficult to comply with PREA, despite considerable efforts [7]. Recent research has demonstrated that far fewer pediatric antibacterial drug trials are conducted relative to studies for other pediatric conditions: less than 1% ( $n = 82/12,703$ ) of all interventional and observational pediatric studies registered in [ClinicalTrials.gov](https://clinicaltrials.gov) between October 2007 and September 2015 examined antibacterial drugs. [Dr. Joshua Thaden, personal communication, December 21, 2017] Limited information exists on the challenges of conducting pediatric clinical trials from the investigators' perspectives, particularly antibacterial drug trials.

The Clinical Trials Transformation Initiative (CTTI), a public–private partnership between the FDA and Duke University, implemented a multifaceted project to address this concern. The project team—comprised of experts from industry, academia, patient groups, and the FDA—conducted several studies to identify the scientific and operational factors involved in conducting pediatric antibacterial drug trials [12]. In this article, we describe the findings from one of those studies: a survey of investigator perceptions of the barriers to and the important facilitators of successful implementation of pediatric antibacterial drug trials.

## 2. Methods

We conducted an online survey (Qualtrics software, Provo, UT) with a convenience sample of investigators of pediatric antibacterial drug trials. Because a record or list of all investigators of pediatric drug trials did not exist, we recruited investigators through professional networking and pediatric member organizations. Members of the CTTI Steering Committee and the project team identified potential survey respondents based on their knowledge of U.S.-based investigators of pediatric antibacterial drug trials. Those investigators, together with members of six sections of the American Academy of Pediatrics (AAP) (Clinical Pharmacology & Therapeutics, Infectious Diseases, Critical Care, Hospital Medicine, Advances in Therapeutics and Technology, and Neonatal-Perinatal Medicine), were sent an email invitation describing the purpose of the online survey and requesting their participation; members of AAP were asked to respond if they had ever conducted a pediatric antibacterial drug trial. Investigators were also asked to forward the survey invitation to other investigators they knew who conduct pediatric antibacterial drug trials. The survey was administered over a 5-week period in August and September 2015.

After asking limited demographic questions, we presented respondents with 15 potential facilitators of successful pediatric antibacterial drug trials, arranged in 5 categories: (1) access to potential study participants, (2) staff support, (3) clinic space, (4) finance, and (5) miscellaneous. Respondents were asked to use a four-point Likert scale to rate the degree of importance of each facilitator: very important, somewhat important, somewhat unimportant, or unimportant. Next, we presented respondents with 36 potential barriers to pediatric antibacterial drug trials, arranged in 6 categories: (1) study protocol, (2) ethics and regulatory, (3) parental concerns, (4) parent and child logistics, (5) concerns of colleagues (i.e., fellow physicians), and (6)

miscellaneous. Respondents were again asked to use a four-point Likert scale to rate the severity of each barrier: major, moderate, somewhat, or not a barrier. All items were identified by the project team members based on their experience with pediatric antibacterial drug trials. By assessing the importance and severity of these potential facilitators and barriers, we aimed to identify which items were perceived by investigators to be the key factors in supporting and impeding the successful conduct of pediatric antibacterial drug trials. Last, we asked respondents to describe the three most significant challenges they have faced in the conduct of pediatric antibacterial drug trials. For all closed-ended questions, respondents could choose “not applicable” if they had not encountered the issue or “not sure” if they were uncertain about the answer. Open-ended questions were also asked throughout, allowing respondents to list other factors encountered when conducting pediatric antibacterial drug trials. No distinction was made between inpatient and outpatient sites for study conduct.

Descriptive statistics were used to summarize the closed-ended questions. For the open-ended questions, we grouped responses by overall themes and then documented the frequency of each theme. We received a determination of exempt status by the Duke University Health System Institutional Review Board. Respondents agreed to participate in the survey by activating the link and initiating the online survey.

## 3. Results

### 3.1. Study population

Of the 101 participants who responded to the survey invitation, 28 were excluded from participating, either because they had not previously conducted a pediatric antibacterial drug trial ( $n = 21$ ) or because they did not answer any question after the demographic section of the survey ( $n = 7$ ). The final sample size was 73.

Many respondents were specialists in pediatric infectious diseases (48%) or neonatologists (23%). The majority had conducted pediatric antibacterial drug trials for more than 10 years (53%) and at academic children's hospitals (88%) (Table 1). Almost all associated hospitals had a neonatal intensive care unit (99%).

**Table 1**  
Respondent characteristics,  $n$  (%).

Variable	$n = 73$
<b>Specialty<sup>a</sup></b>	
Pediatric infectious disease	35 (47.9)
Neonatologist	17 (23.3)
Pediatric intensivist	8 (11.0)
Pediatrician (general)	7 (9.6)
Pharmacologist	7 (9.6)
Pediatric hematologist/oncologist	0 (0)
Other <sup>b</sup>	10 (13.7)
<b>Years conducting pediatric antibacterial drug trials</b>	
Less than 5 years	20 (27.4)
5–10 years	14 (19.2)
More than 10 years	39 (53.4)
<b>Type of facility<sup>a</sup></b>	
Academic children's hospital	64 (87.7)
Large community hospital (e.g. 100 beds)	6 (8.2)
Children's hospital (nonacademic)	4 (5.5)
Private clinic	3 (4.1)
Community clinic	0 (0)
Small community hospital	0 (0)
Other <sup>c</sup>	7 (9.6)

<sup>a</sup> Respondent selected all that applied.

<sup>b</sup> Pediatric hospital medicine, pediatric nephrologist, pediatric clinical pharmacology, clinical pharmacologist, pediatric cardiologist, pediatric emergency medicine, pediatric pulmonologist.

<sup>c</sup> Pediatric clinical research unit/clinical research unit, academic general hospital/medical center, integrated health system.

**Table 2**

Perceptions of factors important to the successful implementation of pediatric antibacterial drug trials, n (%).

Category	Very important	Somewhat important	Somewhat unimportant	Unimportant	Not sure	NA
<b>Access to potential study participants, n = 73</b>						
Being able to recruit potential study patients from my practice	57 (78.1)	11 (15.1)	2 (2.7)	2 (2.7)	0 (0)	1 (1.4)
Having others refer potential patients to your study	38 (52.1)	16 (21.9)	8 (11.0)	7 (9.6)	0 (0)	4 (5.5)
<b>Staff support, n = 73</b>						
Having site research personnel assist with enrolling study patients	70 (95.9)	3 (4.1)	0 (0)	0 (0)	0 (0)	0 (0)
Having staff with expertise in regulatory submissions and follow-up	63 (86.3)	10 (13.7)	0 (0)	0 (0)	0 (0)	0 (0)
Having staff with expertise in developing and negotiating budgets	59 (80.8)	13 (17.8)	1 (1.4)	0 (0)	0 (0)	0 (0)
Having staff with expertise in IRB submission and follow-up	58 (79.5)	14 (19.2)	1 (1.4)	0 (0)	0 (0)	0 (0)
Having adequate administrative support for research-related logistical activities	52 (71.2)	19 (26.0)	1 (1.4)	1 (1.4)	0 (0)	0 (0)
Getting adequate support from clinic or hospital <i>nursing</i> personnel	43 (58.9)	26 (35.6)	3 (4.1)	1 (1.4)	0 (0)	0 (0)
Getting adequate support from clinic or hospital <i>laboratory</i> personnel	33 (45.2)	32 (43.8)	6 (8.2)	2 (2.7)	0 (0)	0 (0)
Partnering with a CRO to facilitate research	21 (28.8)	31 (42.5)	12 (16.4)	6 (8.2)	2 (2.7)	1 (1.4)
<b>Clinic space<sup>a</sup>, n = 72</b>						
Having adequate clinic space for patient study visits	43 (59.7)	21 (29.2)	2 (2.8)	1 (1.4)	0 (0)	5 (6.9)
Having adequate office space for research administration	29 (40.3)	35 (48.6)	8 (11.1)	0 (0)	0 (0)	0 (0)
<b>Finance, n = 73</b>						
Receiving adequate funding from sponsor to cover trial implementation costs other than investigator salaries <sup>a</sup>	69 (95.8)	3 (4.2)	0 (0)	0 (0)	0 (0)	0 (0)
Receiving adequate funding from sponsor for the investigators' salary <sup>b</sup>	45 (63.4)	18 (25.4)	5 (7.0)	3 (4.2)	0 (0)	0 (0)
<b>Miscellaneous<sup>a</sup>, n = 72</b>						
Using electronic data collection and medical record management	35 (48.6)	34 (47.2)	1 (1.4)	2 (2.8)	0 (0)	0 (0)

CRO = contract research organization; NA = not applicable.

<sup>a</sup> Data missing from one respondent.<sup>b</sup> Data missing from two respondents.

### 3.2. Facilitators of the conduct of pediatric antibacterial drug trials

Each factor in all five categories was reported as “very important” or “somewhat important” for the successful implementation of pediatric antibacterial drug trials by a high percentage of participants ( $\geq 70\%$ ) (Table 2). Two factors especially were recognized as “very important” facilitators by almost all respondents (96%): having site research personnel available to assist with enrolling study patients and receiving adequate funding from sponsors to cover trial implementation costs other than investigator's salaries. Among the other top “very important” factors ( $\geq 70\%$ ), four were related to staffing: having staff with expertise in regulatory submissions and follow-up (86%); having staff with expertise in developing and negotiating site budgets (81%); having staff with expertise in IRB submissions and follow-up (80%); and having adequate administrative support for research-related logistical activities (71%) (Table 3). The remaining top factor was being able to recruit potential study patients from the investigators' own practice (78%).

When respondents were asked to identify additional facilitators related to the survey categories, additional factors related to recruitment, staffing, and funding were common. Eight respondents said that having established referral systems, such as interdisciplinary collaborations and access to the hospital inpatient database, were important. Seven said that staff buy-in, “the willingness of other practitioners to allow their patients to enroll,” and having good relationships with those who refer patients were also important factors. Adequate funding, specifically for study staff, was described by seven respondents. A pediatric infectious disease specialist stressed the benefit of having dedicated staff with the “flexibility to enroll the patient with little advance time warning.” Similarly, having staff available 24 h a day, 7 days a week, was also described. A neonatologist said, “For inpatient studies, an innovative way of managing recruitment 24/7 is important. This has been the most challenging.” A pharmacologist said, “Having provision for long-term support of staff so that you are not constantly training new staff for each new study.” Six respondents focused on the importance of adequate study coordinator payment. A pediatric infectious disease specialist said: “Investigators are doing these trials for free. Studies DO NOT have a budget big enough to even offset the cost of the coordinator. The investigator almost always relinquishes investigator earmarked dollars toward coordinators, in order not to lose them.”

**Table 3**Perceptions of factors that are *very important* to the successful implementation of pediatric antibacterial drug trials, n (%).

Factor	n = 73
Having site research personnel assist with enrolling study patients	70 (95.9)
Receiving adequate funding from sponsor to cover trial implementation costs other than investigator salaries <sup>a</sup>	69 (95.8)
Having staff with expertise in regulatory submissions and follow-up	63 (86.3)
Having staff with expertise in developing and negotiating site budgets	59 (80.8)
Having staff with expertise in IRB submissions and follow-up	58 (79.5)
Being able to recruit potential study patients from my practice	57 (78.1)
Having adequate administrative support for research-related logistical activities	52 (71.2)
Receiving adequate funding from sponsor for the investigator salary <sup>b</sup>	45 (63.4)
Having adequate clinic space for patient study visits <sup>a</sup>	43 (59.7)
Getting adequate support from clinic or hospital <i>nursing</i> personnel	43 (58.9)
Having others refer potential patients to your study	38 (52.1)
Using electronic data collection and medical record management <sup>a</sup>	35 (48.6)
Getting adequate support from clinic or hospital <i>laboratory</i> personnel	33 (45.2)
Having adequate office space for research administration <sup>a</sup>	29 (40.3)
Partnering with a clinical research organization to facilitate the research	21 (28.8)

IRB = institutional review board.

<sup>a</sup> Data missing from one respondent.<sup>b</sup> Data missing from two respondents.

### 3.3. Barriers to the conduct of pediatric antibacterial drug trials

Each factor in all six categories was rated as a barrier (“somewhat,” “moderate,” or “major”) by a considerable percentage of participants (range: 48.5%–98.6%) (Figs. 1 and 2). In comparison with the other categories, almost all of the factors in the parental concern category were identified as a barrier by a high percentage of respondents ( $\geq 80\%$ ); factors in the concerns of colleagues category were identified as barriers by a lower percentage of respondents compared to the other categories.

Focusing on the “major” barriers, four factors were identified by a higher percentage of participants compared with other factors. Three of

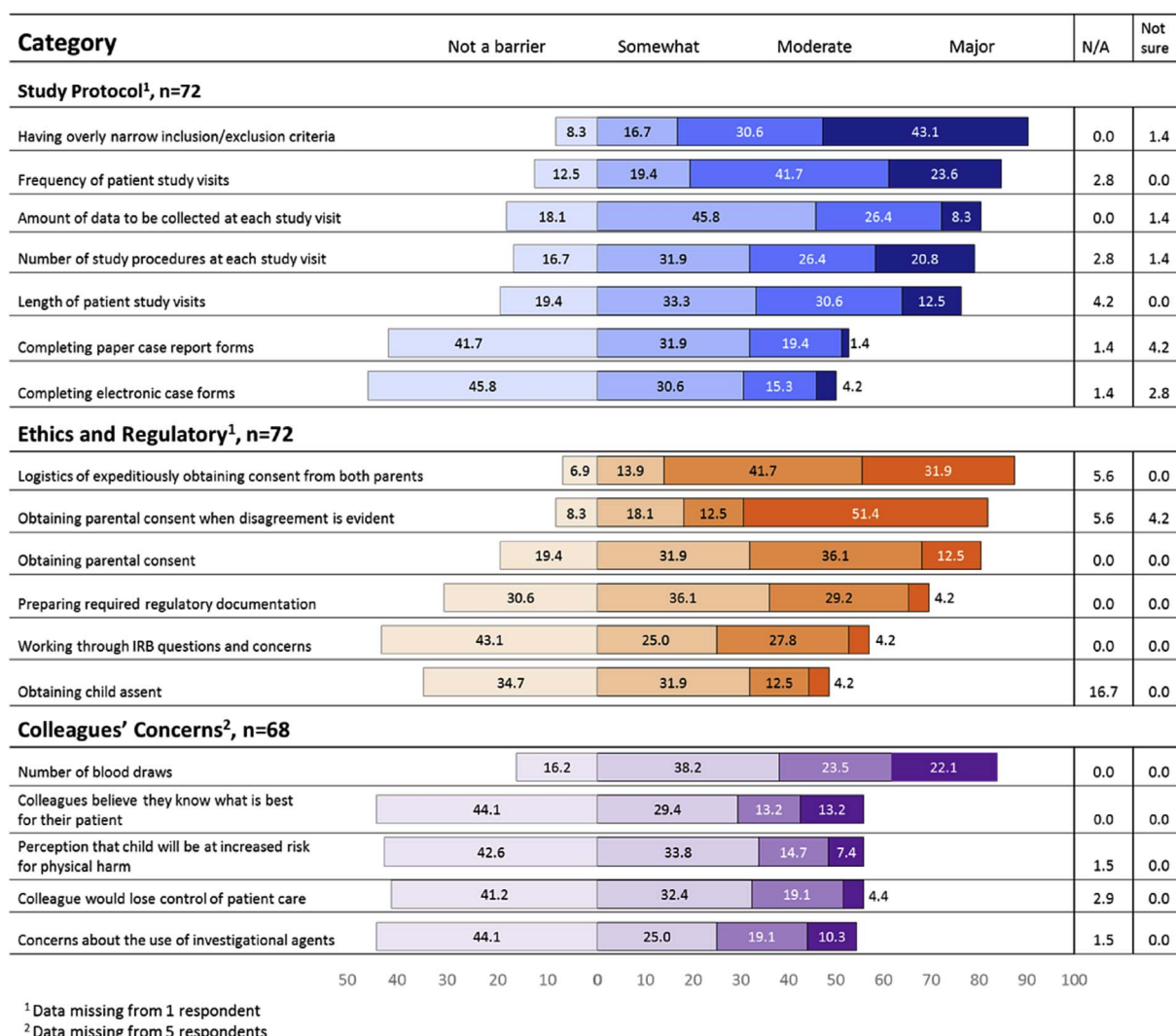


Fig. 1. Perceptions of potential barriers related to pediatric antibacterial study protocols, ethics and regulatory processes, and colleagues' concerns about pediatric antibacterial trials, %.

these were related to parental involvement and consent: obtaining parental consent when disagreement between parents is evident (51%), concerns about the number of blood draws (47%), and concerns about the number of invasive procedures (44%). The remaining major barrier was having overly narrow inclusion/exclusion criteria (43%) (Figs. 1 and 2).

### 3.4. Top challenges highlighted by respondents

From the open-ended responses, we identified three main themes on the most significant challenges respondents ( $n = 59$ ) experienced in conducting pediatric antibacterial drug trials.

Trial finances were mentioned most often ( $n = 27$ ). Respondents stressed that budgets were insufficient to cover trial costs. A few described the difficulties caused by inadequate funding, such as a pediatric pharmacologist who said “finding study coordinators with sufficient experience given the meager remuneration afforded from the low-cost studies” was a significant challenge. A pediatrician explained that inadequate funding has led to the “inability to compensate study staff adequately for their time and expertise.”

The difficulties investigators faced in identifying, recruiting, and efficiently enrolling the necessary number of eligible patients were also frequently described ( $n = 23$ ). Many focused their responses on their inability to enroll sufficient numbers of patients because of overly narrow inclusion and exclusion criteria. For example, a pediatric

infectious disease specialist said, “very narrow inclusion/exclusion criteria make it inefficient to screen patients unless financial support is sufficient.”

Last, parental consent was identified by many respondents ( $n = 20$ ). A few explained that the requirement for documenting informed consent from two parents and the lack of direct benefit to the child from study participation made obtaining parental consent difficult. A neonatologist described this challenge as “obtaining consent when the parents see no direct benefit for their child and are happy with current care.”

## 4. Discussion

Our purpose in conducting this survey was to identify—from the perspective of pediatric investigators who conduct antibacterial drug trials—the key factors that contribute to the successful implementation of such trials and the key barriers that make implementation difficult. Our findings demonstrate that a high percentage ( $\geq 70\%$ ) of respondents agreed that the 15 potential facilitators presented were important (“very” or “somewhat”) to success. Further, several barriers highlighted by respondents provided critical insights into their current challenges, demonstrating the complex nature of conducting such trials.

To begin to address these challenges, it is important to both enable the most significant facilitators and remove the major barriers. Several areas provide opportunities to focus effort. The first area is improved



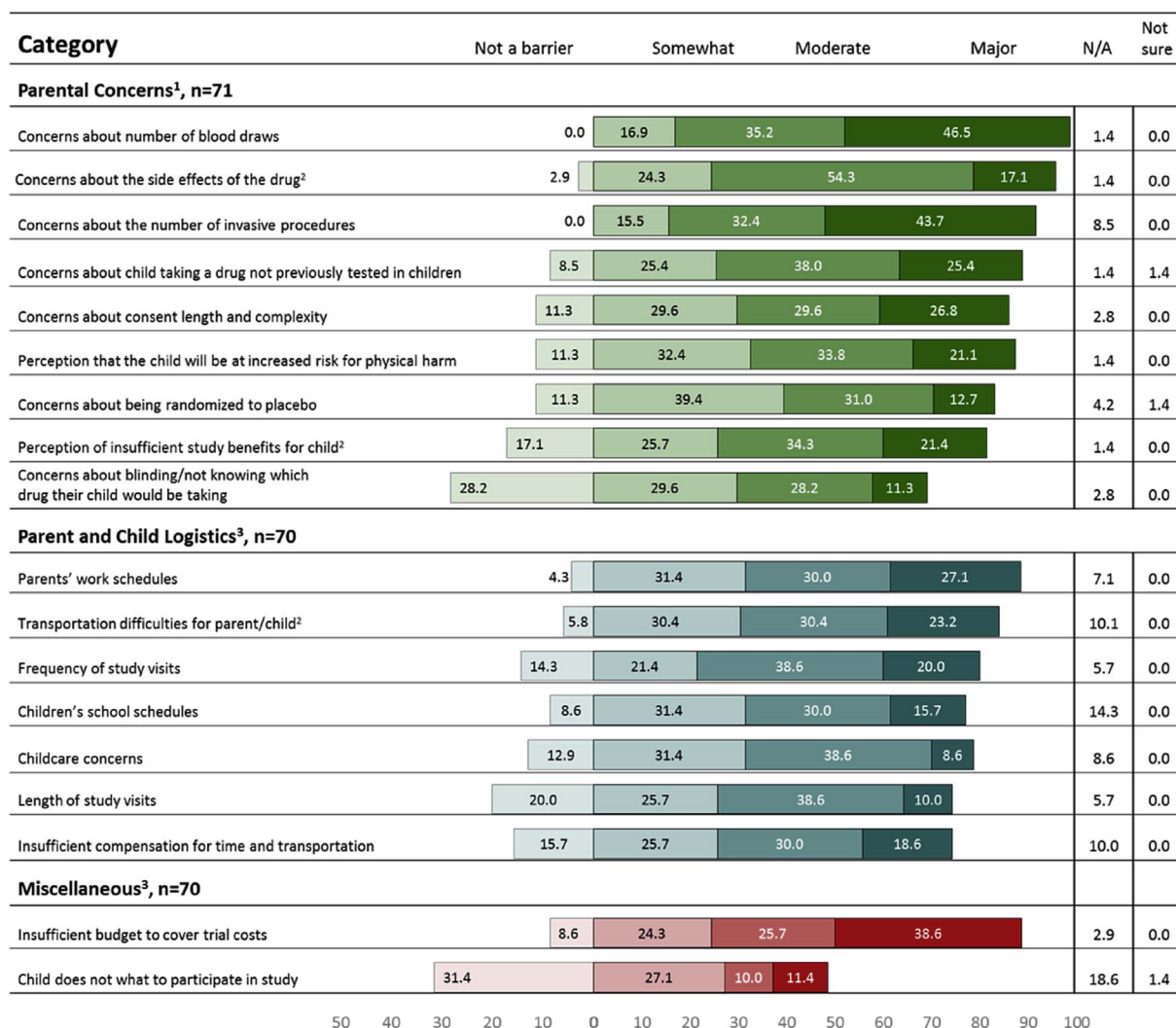
<sup>1</sup> Data missing from 2 respondents<sup>2</sup> Data missing from 1 respondent<sup>3</sup> Data missing from 3 respondents

Fig. 2. Perceptions of potential barriers related to parental concerns and parent or child logistics.

engagement with parents of children who may be eligible to enroll in a pediatric antibacterial drug trial. Investigators should consider how to address the parental concerns identified in this survey when designing their trials, such as reducing the number of blood draws where possible. It is also the investigator's responsibility to communicate information about a trial and its implications in the most effective and understandable way so that parents can make an informed decision about their child's participation. Parents need to understand clearly the potential benefits and risks so they can make the best decision for their child. However, even with effective communication, parents still may be only willing to accept a minimal level of risk to their child's health, making the implementation of some trials challenging.

A second area of effort involves the recognition that strict eligibility criteria have a negative impact on trial enrollment. Sponsors and investigators should consider situations where broader inclusion criteria could apply, including allowing for some effective antibacterial drugs prior to enrollment, and where trials can be streamlined. However, the safety of antibacterial drugs for all pediatric age groups is important to evaluate, mandating that reasonable data be collected on clinical and laboratory adverse events, in addition to clinical and microbiologic outcomes. Even with attempts to streamline trials, some studies may simply take longer to enroll, particularly for the youngest age groups.

The third area of effort involves staffing and financial strategies. There is value in setting up and funding pediatric trial networks that can help facilitate ongoing drug development and also eliminate the need for startup with each new trial. Trial networks can help to standardize the requirements for site resources and funding. A last funding consideration is that sites must submit realistic budgets that will fully support the staffing necessary for success—and sponsors likewise should be prepared to fund these trials with realistic costs.

We acknowledge that our findings are preliminary given our sampling strategy. We would have preferred to sample a definitive group of investigators of pediatric antibacterial drug trials, but such a group does not exist to our knowledge. We therefore attempted to reach as many investigators as possible. Nevertheless, our findings provide insight into the facilitators and challenges experienced by investigators of pediatric antibacterial drug trials and can help to focus efforts to encourage the conduct of such trials.

While investigators of pediatric antibacterial drug trials face many challenges, they are keenly aware of the factors that can lead to successful implementation. The pediatric antibacterial drug trials enterprise can likely benefit from focused efforts by all stakeholders in drug development and approval that will remove barriers, expand and enable facilitators, and engender the crucial support of trial sponsors.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.conctc.2018.01.003>.

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